REMARKS

Status of the Claims

Claim 6 is pending and is rejected herein. Claim 6 is amended. Claims 1-5 and 7 are canceled. No new matter is added.

Amendments to the claims

Claim 6 is amended to overcome the 35 U.S.C. §103(b) rejection as discussed *infra*. Amended claim 6 clarifies that the particle comprising an antibody/fragment and a pharmaceutical is made of biodegradable polymers or PEGylated copolymers and, therefore, is distinct from a liposome (pg. 24, ll. 11 to pg. 25, ll. 15). The specification teaches that a biomolecular carrier may be biodegradable particles, liposomes, microbubbles, polymersomes, and synthetic secretory granules (pg. 20, ll. 2-5; pg. 35, ll. 18 to pg. 36, ll. 2). No new matter has been added.

The 35 U.S.C. §103(a) rejection

Claim 6 is rejected under 35 U.S.C. §103(a) as being unpatentable over **Hallahan** *et al.* (U.S. 6,159,443), in view of **WO 98/53852**, the known fact disclosed in the specification on pages

4, lines 15-20; 5, lines 1-5; and 10, lines 12-20, and **Mastrobattista** *et al.*, (*Biochim. Biophys. Acta*, 1999, 1419: 353-363). This rejection is respectfully traversed.

The Examiner states that **Hallahan** *et al.* teach a method of treating cancer by exposing a target tissue or organ to the ionizing radiation and administering P-selectin antibody labeled delivery vehicle that carry active agent to the tumors (Abstract, col. 6, ll. 5-30; col. 13, ll. 24-30). The Examiner also states that **Hallahan** *et al.* teach a radiation-induced increase in P-selectin in irradiated tumor and that the use of radiation to control cellular adhesion molecules is a unique approach to the treatment of tumors (col. 6, ll. 5-15).

The Examiner states that **WO 98/53852** teaches that exposing tissue to irradiation causes an increase in expression of several cell adhesion molecules including ELAM-1, E-selectin and ICAM-1 in endothelial cells (pg. 2, ll. 15-25; pg. 3, ll. 1-10). The Examiner also states that the instant Specification teaches that exposure of normal and diseased tissue to irradiation causes an increase in leukocyte infiltration due to the adhesion of leukocytes to the microvascular endothelium which has increased expression of

CAMs such as E-selectin, P-selectin and ICAM-1 (pg. 4, ll. 3-30; pg. 5, ll. 1-5; pg. 10, ll. 12-20).

Thus, the Examiner states that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of **WO 98/53852**, **Mastrobattista** *et al.* and the known fact disclosed in the Applicants' specification to **Hallahan** *et al.* and substitute biomolecular carrier bearing antibodies to the cellular adhesion molecule P-selectin to a biomolecular carrier bearing antibodies to another cellular adhesion molecule, ICAM-1, since the expression of any one of them would be enhanced in target tissue after irradiation and obtain Applicants' claimed method of treating cancer.

The Examiner states that motivation is found in that the Applicants' specification teaches that exposure of normal and diseased tissue to irradiation causes an increase in leukocyte infiltration which adhere to the microvascular endothelium. Also, **WO 98/53852** teaches irradiating tissue increases expression of several cell adhesion molecules including P-selectin, E-selectin and ICAM-1 in endothelial cells. Furthermore, the Examiner states that **Hallahan** uses a P-selectin labeled delivery vehicle to target cancer

tissue or organ where irradiation increased expression of P-selectin. Finally, **Mastrobattista** *et al.* use a biomolecular carrier bearing antibodies to another cell adhesion molecule ICAM-1 to deliver drugs to the sites where the expression of ICAM-1 is increased.

Applicants' maintain that **Mastrobattista** *et al.* specifically teach that ICAM-1 targeted immunoliposomes bind to bronchial epithelial cells *in vitro* in a concentration dependent manner, **Mastrobattista** *et al.* may be used as carriers for the intracellular delivery of anti-inflammatory drugs to sites of inflammation characterized by an increased expression of ICAM-1 (Abstract).

Hallahan *et al.* teach an x-ray guided delivery vehicle, which carries an active agent, that binds to activated platelets that is preferably a platelet or a leukocyte or, more preferably, is a protein/peptide, an antibody, a microsphere coated with a protein/peptide or a liposome conjugated to platelets, leukocytes, or proteins/peptides (Abstract; col. 7, ll. 37 to col. 8, ll. 10). **Hallahan** *et al.* further disclose that a radiation-induced increase in P-selectin resulted in platelet aggregation which express GP-IIb, GP-IIIc and P-selectin antigens (col. 6, ll. 6-18). Thus, **Hallahan** *et al.*

teach a method of selectively targeting tumors by delivering radiation to target tumors to induce platelet aggregation in tumors and using delivery vehicles which bind activated platelets to carry active agents to the tumor (col. 6, ll. 18-23).

As amended and discussed *supra*, Applicants' invention is drawn to a method of treating cancer by irradiating the cancerous tissue/organ and administering a particle of biodegradable polymers or PEGylated copolymers comprising an antibody/Ab fragment that binds to ICAM-1 on endothelial cells and a pharmaceutical.

In a prima facie case of obviousness, the combination of the references must teach all the elements of the invention. Additionally, one must consider what is fairly taught in the combination of references. First, the Examiner asserts that in considering the combination of the prior art and what is known in the art, one of ordinary skill in the art would be motivated to modify **Hallahan** to substitute biomolecular carrier bearing anti-P-selectin antibodies to a biomolecular carrier bearing anti-ICAM-1 antibodies because, *inter alia*, **Hallahan** uses a P-selectin antibody labeled delivery vehicle carrying an active agent to target cancer tissue.

What **Hallahan** *et al.* fairly teach is targeting activated platelet antigens, such as GB IIb and GB IIIa, with a delivery vehicle that preferably is an antibody, a microsphere coated with a protein/peptide or a liposome conjugated to platelets, leukocytes, or proteins/peptides. **Hallahan** *et al.* also fairly teach that P-selectin is sequestered within storage reservoirs within endothelial cells and within alpha granules in platelets (col. 5, ll. 27-29) and the expression of both contribute to the increase in endothelial lumenal P-selectin upon tissue irradiation (col. 3, ll. 43-44).

What **Hallahan** *et al.* do not fairly teach is targeting P-selectin antigens either on activated platelets or on the endothelial lumenal surface. In fact **Hallahan** *et al.* only present a protocol for targeting radiolabeled anti-P-selectin antibodies to P-selectin in blood vessels to treat angiogenesis. Furthermore, should one of ordinary skill in the art administer an anti-P-selectin antibody, **Hallahan** *et al.* provide no guidance that the P-selectin platelet antigen would not compete for the antibody and, therefore, one of such skill would only be trying in following the protocol presented.

The Examiner states that further motivation is found in **Hallahan** *et al.* disclosing biodegradable particles such as

microspheres or liposomes as delivery vehicles (col. 7, ll. 45-65) and that the instant Specification discloses liposomes as examples of biodegradable particles (pg. 11, ll. 3-20). **Hallahan** *et al.* disclose that microspheres or liposomes are bio-compatible particles that may be adapted for preferential binding to activated platelets by coating or otherwise adhering a peptide or antibody specific for platelets thereto. The preferred delivery vehicle disclosed in **Hallahan** *et al.* is fibrinogen-coated microspheres which binds strongly to platelet antigens GB IIb/GB IIIa (col. 7, ll. 65 to col. 8, ll. 10).

Contrary to the Examiner's assertion, Applicants define particles, as is known in the art, as microspheres and nanospheres which are distinct from liposomes. The specification defines a biodegradable particle as comprising biodegradable polymers or PEGylated copolymers (pg. 24, ll. 11 to pg. 25, ll. 15). Biodegradable particles are only one kind of drug carrier. Other classes of carriers include liposomes, microbubbles, polymersomes or synthetic secretory granules (pg. 28, ll. 17-20).

Applicants acknowledge that it is known in the art that drug carriers, such as microspheres or liposomes, may be adapted

to target a specific cell or tissue. However, it is not obvious that these carriers are interchangeable as drug delivery vehicles. In fact **Mastrobattista** *et al.* teach that even specific binding of an immunoliposome to its target cell is not enough for effective drug delivery. One must consider whether the immunoliposomes will be internalized, liposome size, type of cell and type of target receptor (pg. 354, col. 1, 2nd paragraph). At best the combination of **Hallahan** *et al.*, **WO 98/53852**, **Mastrobattista** *et al*, and what is known in the art, would suggest to or motivate one of ordinary skill in the art to administer an anti-ICAM-1 immunoliposome comprising an active agent to irradiated tumor tissue. This is not Applicants' invention.

Furthermore, **Mastrobattista** *et al.* teach that ICAM-1 is expressed constitutively on vascular endothelial cells, epithelial cells and on leukocytes and its expression is increased in the presence of pro-inflammatory cytokines (pg. 354, col. 1, ll. 1-5). **Mastrobattista** *et al.* demonstrate the specific binding of anti-ICAM-1 immunoliposomes to ICAM-1 on bronchial epithelial cells *in vitro*. In administering an anti-ICAM-1 immunoliposome to irradiated tumor tissue *in vivo*, one of ordinary skill in the art would

not know if leukocytes expressing ICAM-1 would compete for the immunoliposome and prevent or minimize drug delivery to the tumor tissue.

Applicants demonstrated that no adhesive interactions between anti-ICAM-1 coated microspheres and leukocytes occurred *in vivo* (pg. 28, ll. 1-12). As such, to substitute a biodegradable particle, as defined in the instant Specification, for the liposome, one of ordinary skill in the art certainly would only be trying with no reasonable expectation of success for the reasons presented *supra*. Obvious to try has long been held not to be the standard for obviousness.

Thus, Applicants submit that, as a teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure, a *prima facie* case of obviousness has not been established. Accordingly, in view of the arguments presented *supra*, Applicants' respectfully request that the rejection of claim 6 under 35 U.S.C. 103(a) be withdrawn.

This is intended as a complete response to the Office Action mailed March 25, 2004. If any issues remain outstanding, the Examiner is respectfully requested to telephone the attorney of record identified below for immediate resolution. Applicants enclose a Petition for Extension of time; any applicable fees should be charged to Deposit Account No. 07-1185.

Respectfully submitted,

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